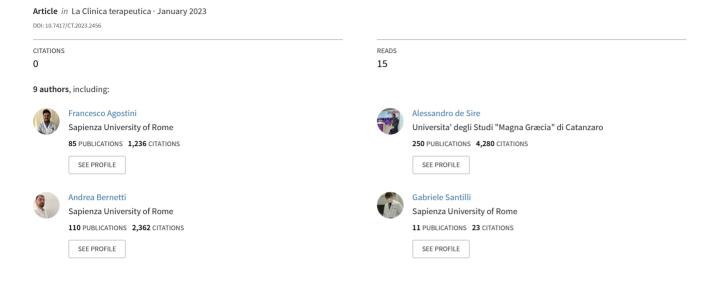
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Effectiveness of Kinesiotaping and McConnell taping combined with physical exercise on gait biomechanics in patients with patellofemoral syndrome: non-randomized clinical trial



# Effectiveness of Kinesiotaping and McConnell taping combined with physical exercise on gait biomechanics in patients with patellofemoral syndrome: non-randomized clinical trial

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#### Abstract

*Background*. Patellofemoral pain syndrome (PFPS) is a pathological condition of the knee, typical of young adults, characterized by diffuse pain in the anterior and / or medial part of the knee. We aimed to examine the effectiveness of the two types of taping in association with therapeutic exercise in relation to the biomechanical parameters, on pain and on functionality of the lower limb in patients with PFPS.

*Methods.* We collected data from patients treated in our outpatient's clinic with two kinds of bandage: the Kinesiotaping group (KG) and the McConnel taping group (MG). All subjects were evaluated trough an optoelectronic system, the Numeric Pain Rating Scale (NPRS), and with the Lower Extremity Functional Scale (LEFS) at baseline before applying the taping (T0), fifteen minutes after applying the bandage (T1), after four weeks of treatment (T2) without applying the bandage and three months after the end of the first treatment period with bandages and exercises (T3).

*Results.* Thirty-five patients (KG 16; MG 19) were included in the study. The most statistically significant changes over time in the LEFS and NPRS values have been recorded in the MG group compared to KG. The average speed and hip rotation showed a statistically significant increase between T3 and T0.

*Conclusion.* The application of the knee bandage for PFPS would appear to show improvement in NPRS and LEFS outcomes in both groups. Furthermore, in this study the MG evidenced better results and significant changes over time than KG. *Clin Ter 2023; 174 (5):395-403 doi: 10.7417/CT.2023.2456* 

**Key words**: Patellofemoral syndrome, Rehabilitation, Taping, Knee, Biomechanics

## Introduction

Patellofemoral pain syndrome (PFPS) is a pathological condition of the knee, typical of young adults, characterized by diffuse pain in the anterior and / or medial part of the knee that presents with activity under load and in flexion of the knee (1). In a recent consensus it was established that the main criterion for defining it, is peri or retro-patellar pain that is aggravated by activities that overload the patellofemoral joint with the knee flexed (for example, squatting, climbing, or descending the stairs, jogging, running, jumping) (2). Additional but not essential criteria are joint squalls during flexed knee activities, tenderness on palpation of the patellar facets, slight effusion, pain with prolonged sitting and transition from sitting to standing position (1). It has been estimated that about 11-17% of young patients who go to a specialist for knee pain suffer from PFPS and 25-40% of sportsmen are affected (2). This syndrome occurs more frequently in the sports population, in fact 25-40% of sportsmen are affected (2). Among genders, females are twice likely to develop PFPS as much as compared to males (3). PFPS has a multifactorial etiology (4). The triggers can be divided into local joint factors, such as altered patellar tracking with patellar hypermobility (5), altered activation times of the vastus medialis (VM) compared to the vastus lateral (VL) and hypotrophy of the vastus medialis oblique (VMO) (6), retraction of the iliotibial band, quadriceps femoris, hamstrings and gastrocnemius (7), and general factors, such as weakness of the abductor and extra rotator muscles of the hip, altered position of the foot (8). These factors therefore contribute to alter the physiological biomechanics of the lower limb (9). Some studies have shown that patients with PFPS are more often affected by psychological disorders such as anxiety, depression, kinesiophobia and addiction than patients in the control group (10). The diagnosis of

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PFPS is mainly clinical and is based on medical history and on an accurate physical examination (10). Usually, imaging is not required to diagnose PFPS. In a recent meta-analysis (2016) it was highlighted that on magnetic resonance imaging it is possible to recognize some typical features of the PFPS: increase in the bisect-offset under load with knee at 0°, tilt of the patella and contact of the patello-femoral area) (11). Treatments involves a conservative and a surgical approach. The conservative approach of PFPS provides for different modalities, but therapeutic exercise is the one that presents the most evidence in the literature (2). In fact, most of the studies, underline the importance of therapeutic exercise in the short, medium, and long-term benefits, for the reduction of pain and the improvement in functional skills (12-15). Therapeutic exercise includes strengthening exercises for the proximal hip muscles (abductors and external rotators), quadriceps femoris, core stability as well as specific stretching exercises (16). Taping is a recent technique, and the two most used methods are McConnell taping and Kinesiotaping (17, 18). Operation and application are different: the first acts on the imbalance between VMO and VL, while the second stabilizes the patella by medializing it. Both, however, were effective in terms of pain reduction, in association with therapeutic exercise (19). There is little evidence in the literature about the use and effectiveness of instrumental physical therapy (ultrasound, laser, NMES, TENS and biofeedback) (20). Also, regarding orthoses, there are

few studies that show the effectiveness of their use in PFPS compared to other treatments. The most used orthoses are knee pads, to change the position of the patella, or custom-made insoles to correct foot anomalies (21). The aim of the study is to examine the effectiveness of the two types of taping in association with therapeutic exercise and to verify how they act in the short, medium, and medium-long term in relation to the biomechanical parameters of walking, on pain and on the overall functionality of the lower limb in patients with PFPS.

## Methods

In this non-randomized clinical trial, we included patients from the Physical and Rehabilitative Medicine Outpatient Clinic of the "Umberto I" University Hospital in Rome with a clinical and radiological diagnosis of PFPS in the period between October 2021 and January 2022. The inclusion criteria were subjects aged between 18 and 50 years, with symptoms of PFPS for at least one month diagnosed clinically and / or documented by relative imaging. Subjects with neurological or rheumatological pathologies, trauma to the lower limbs, recent orthopedic surgery, diabetes, neoplasms or taking pain-relieving drugs were excluded. The selected subjects were divided in two treatment groups based on medical prescriptions. We collected data from patients treated in our outpatient's clinic with two kind of knee bandage for 4 months: the Kinesiotaping group (KG) and the McConnel taping group (MG). Both groups performed, after an adequate training, a strengthening and stretching exercise program for a total period of 4 months. The study was conducted in accordance with Helsinki ethical standards. Patients were informed about the possible side effects of the treatment. All patients signed informed consent forms. The reporting of this study followed the STROBE guidelines.

#### Taping

Kinesiotaping was administered to KG. It was introduced by Kenzo Kase in 1990 and it consists of an adhesive cotton bandage with elastic properties. There are several types of applications widely described in the literature (17). The chosen application (the simplest one to reproduce at home by the patient in autonomy) consists of an inverted Y with an approximate length of 20-25 cm (depending on the anatomical characteristics of the patient) of 10-15% tension (without tension) for the stimulation of the muscle bellies of the quadriceps muscle (VM, VL) (Fig. 1A).

McConnel taping was administered to MG. It was proposed for the first time in 1984 by Jenny McConnell and it has the rationale of correcting the lateral position of the patella by medializing it. It involves the use of a rigid bandage to perform the medial glide maneuver (Strappal®)



Fig. 1. A. Application of Kinesiotaping (inverted Y); B. Application of McConnell taping

was used), applied over a layer of neutral tension skin protection (Hypafix® was used) to avoid complications such as reactions allergies or friction between the skin and the rigid bandage. Both before and after applying the skin protector, the subjects were taught how to draw the edges of the patella to facilitate the execution of the bandage (Fig. 1B). All patients, after being instructed in the application of taping, performed the bandage for 4 weeks and the patients in group 1 were able to change the material of the bandage every 3-4 days while the subjects in group 2 had to change it every day.

## Physical exercise

The exercises chosen for this study include four strengthening and three stretching exercises. The four strengthening exercises were: 1) Supine quadriceps isometry; 2) Leg elevation to knee extended from supine; 3) Seated knee extension and 4) Squat up to 90° with the use of a TheraBand to stimulate the hip abduction. The three stretching exercises were: 1) Prone quadriceps stretch; 2) Supine hamstring stretch and 3) Standing ilio-tibial band stretch. The exercises were taught to the patients after the first evaluation, and they were given a booklet containing the explanation of the exercises with the corresponding images. Both groups performed the exercises daily for 4 months, both during the period of application of the bandage and after the interruption.

#### Evaluations

All subjects were evaluated using an instrumental analysis of the movement through an optoelectronic system (gait analysis), the Numeric Pain Rating Scale (NPRS) to assess pain, and with the Italian version of the Lower Extremity Functional Scale (LEFS) for evaluating the functionality of the knee and the entire lower limb (22). All subjects were assessed at baseline before applying the taping (T0), fifteen minutes after applying the bandage (T1), after four weeks of treatment (T2) without applying the bandage and three months after the end of the first treatment period with bandages and exercises (T3).

Gait analysis involved assessing kinematic, kinetic, and dynamic parameters (23). Patients were requested to walk at a self-selected speed along a ten meters level surface after applying on their body several retroreflective spherical markers, following the Davis protocol, to determine the joint centers and segment axis (24). The walk was repeated five times. Data collection and analysis was performed using the ELITE system (BTS, Milan, Italy), with eight infrared video cameras (TVC, BTS, Milan, Italy) for the acquisition of the kinematic and kinetic variables. Two Kistler platforms (Kistler Instruments, Winterthur, Switzerland) were employed to acquire the ground reaction forces (GRF) (25). NPRS is a pain assessment scale in which patients select a value for the intensity of their pain that is in a range from 0 to 10, where 0 corresponds to "no pain" and 10 to " worst pain experienced in one's life ". The patient can only select whole numbers.

The LEFS (22, 26) consists of a questionnaire of 20 items that investigate the degree of difficulty in performing a series (5) of daily life activities that involve the use of

the lower limb. Each item has 4 answers for the difficulty reported in the different activities: extreme difficulty (0 points), high difficulty (1), medium difficulty (2), low difficulty (3), no difficulty (4). The score that can be obtained ranges from 0 (low level of functionality) to 80 (high level of functionality).

#### Statistical analysis

We performed a Kolmogorov-Smirnov Test which showed that all variables are not normally distributed. Statistical analysis was conducted using the SPSS version 2.0 analysis program. Values of p <0.05 were considered statistically significant. p <0.05. Descriptive analysis of the sample (baseline: age, sex, affected side) was performed using the Mann-Whitney U test for continuous variables (age) and the square test for categorical and ordinal variables (sex and affected side), to verify or not the homogeneity of the two groups. Non-parametric tests were used for the gait analysis, LEFS and NPRS data due to the small sample size. The Mann-Whitney U test, taking into account the deltas (i.e., variations over time), it was used in order to analyze the possible presence of statistically significant differences between the two groups. Instead, Friedman's repeated measures test was used to analyze whether, regardless of the type of treatment, there were statistically significant differences over time.

#### Results

Forty-five subjects were recruited, of which thirty-five (KG 16; MG 19) included in the study. There were six dropouts at T3, of which two belonged to KG and four MG. At baseline the two groups were found to be homogeneous for age, sex, affected side, LEFS (T0) and NPRS (T0) (Table 1). Through the Shapiro-Wilk's test of normality (p> 0.05), the normal distribution of the data was analyzed. The homogeneity of the variance (p> 0.05) and of the covariance (p> 0.05) was found by means of the Levene's test of homogeneity of homogeneity of the variance (p> 0.05) was found by means of the Levene's test of homogeneity of homogeneity of the variance (p> 0.05) was found by means of the Levene's test of homogeneity of homogeneity of the variance (p> 0.05) was found by means of the Levene's test of homogeneity of homogeneity of the variance (p> 0.05) was found by means of the Levene's test of homogeneity of homogeneity of the variance (p> 0.05) was found by means of the Levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was found by means of the levene's test of homogeneity of the variance (p> 0.05) was

Table 1. Descriptive characteristics of patients included.

	KG	MG	P value
Age (Average ± SD)	30.4 ± 11.7	30.79 ± 13.14	0.9273
Sex (F/M)	12/4 (34.29%)	14/5 (40%)	0.9293
Side (R/L)	7/9 (20%)	10/9 (28.57%)	0.600472
LEFS T0 (Average ± SD)	52.31 ± 7.86	52.74 ± 11.12	0.8990
NPRS T0 (Average ± SD)	6.86 ± 2.25	6.11 ± 1.33	0.2177

Legenda. KG: Kinesiotaping group; MG: McConnel taping group; LEFS: Lower Extremity Functional Scale; NPRS: Numeric Pain Rating Scale.

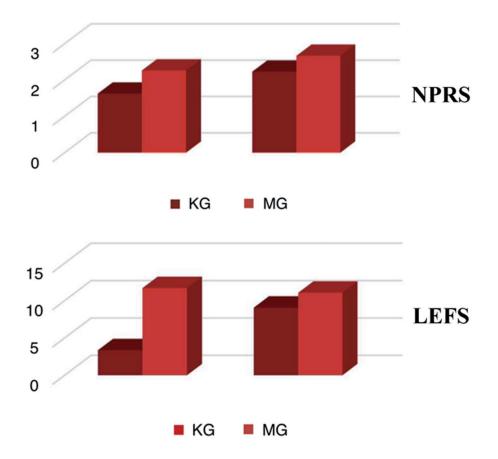


Fig. 2. Differences in time (ΔT) of Numeric Pain Rating Scale (NPRS) and Lower Extremity Functional Scale (LEFS).

neity and the Box's M test, respectively for the variance and for the covariance. The analysis between the two groups did not find statistically significant differences either for the gait analysis data or for the LEFS and NPRS data (Table 2 and Table 3), in fact no p is < 0.05. It can be observed that the most significant changes over time in the LEFS and NPRS values have been recorded in the MG group compared to KG (Fig. 2). Statistically significant data were also found in the gait analysis as regards the average speed and for the ROM of hip rotation with a p <0.05 (Table 2 and Fig. 3), while both the LEFS and NPRS values both achieved statically significant improvement of significant p <0.01 (Table 3 and Figure 3) in both groups. In particular, the average speed and ROM of hip rotation (Table 4) showed a statistically significant increase between T3 and T0. For LEFS and NPRS, this statistically significant increase is evident between T2 and T0 and between T3 and T0 (Table 5).

#### Discussion

In this study, the biomechanics effects on walking of two different bandaging methods (Kinesiotaping and McConnell taping) associated with therapeutic exercise were examined. The first type of bandage acts on the imbalance between VMO and VL, while the second stabilizes the patella by medializing it. Although the rationale of the two bandages is different, it has been seen that both allow a reduction in pain, resulting in an improvement in motor activities and quality of life (19). From the comparison of the two groups before and after the treatment, no statistically significant differences were found. Instead, conducting a statistical analysis within the groups to study the effect of the treatment regardless of the type of bandage, two statistically significant values were observed in the medium / long term: the average walking speed (increased) and the ROM rotation of the hip (decreased).

In a 2016 literature review (27), it was observed that subjects with PFPS have different biomechanical parameters altered both in walking and in other motor tasks (squat, running, jumping), compared to healthy subjects. The altered parameters are reduction in speed, reduced duration of the swing, reduction in cadence, reduction of the knee extension moment in the load and take-off phase. The authors conclude that these gait alterations may be related to a compensatory strategy to reduce the reaction forces in the patellofemoral joint and pain. Alterations were also observed in another systematic review (28) that reported a reduction in speed, a delayed hindfoot eversion peak and an increase in hindfoot eversion during the initial contact phase.

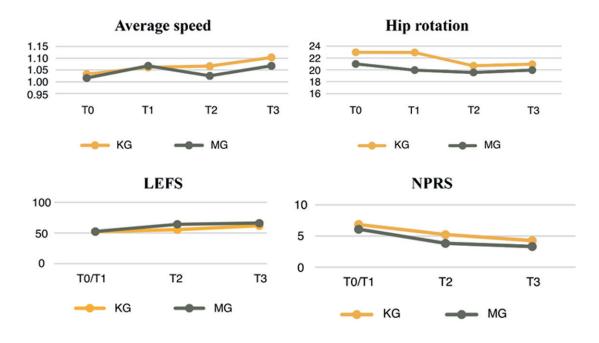


Fig. 3. Average speed, Hip rotation, Lower Extremity Functional Scale (LEFS) and Numeric Pain Rating Scale (NPRS) trend.

There are several studies that analyze the effectiveness in terms of pain and functionality of the application of patellar taping in the PFPS (29). It was also observed how the combination of strengthening and stretching exercises associated with the use of taping lead to a better outcome than the same therapies taken individually (17, 30). Patellar taping is also recommended, among other treatments, with Grade B in the Clinical Practice Guidelines of the Academy of Orthopaedic Physical Therapy of the American Physical Therapy Association (2019) concerning PFPS (31).

Wen-Dien Chang et al. (2015), in a systematic review and meta-analysis (19), observed an improvement in muscle activity and quality of life as pain is reduced using the two types of bandages. McConnell taping modifies patellar alignment but does not improve proprioception and motor functions, unlike Kinesiotaping.

Although therapeutic exercise appears to be the most effective treatment for PFPS, a standardized protocol is not known in the literature, however in some studies it is highlighted as exercises for the proximal hip muscles (abductors and external rotators) when associated with muscle strengthening. quadriceps femoris are more effective than performing quadriceps exercises alone (2, 16, 32-35). The knee extensor muscles can be recruited into both open and closed kinetic chains (Figure 3); Best results are obtained with both types of exercises (12, 36-38). Those in a closed kinetic chain should be carried out between  $0^{\circ}$  and  $45^{\circ}$  of flexion while those in an open kinetic chain between  $45^{\circ}$  and  $90^{\circ}$ , in such a way as to reduce patellar-femoral stress (8). Some exercises in a closed kinetic chain, such as the

squat, are exercises that allow the activation of both the quadriceps and the hip muscles (2). There is also evidence regarding core stability exercises: it has been shown that they can reduce stress by improving lumbo-pelvic stability (35). Stretching the knee and hip muscles, including quadriceps, hamstring, and tensor fascia lata, is effective for improving knee function and ROM and for reducing pain when used in addition to strengthening exercises (39).

In our study, in the light of previous studies, walking speed is one of the parameters that has been found to be altered in subjects suffering from PFPS and that we have observed to increase after administration of the bandage and exercises. Probably the treatment used in the two groups allowed to reduce the reaction forces within the patellofemoral joint. Also, regarding pain, no statistically significant differences were found between the two groups before and after treatment. However, within the groups, regardless of the type of treatment, the subjects reported both a reduction in pain and an increase in lower limb function in the medium and medium-long term. In any case, from the analysis of data relating to functional recovery and pain reduction, a better trend was found in group 2; in fact, the time's variations time between T2 and T0 and between T3 and T0 of the LEFS and NPRS of the McConnell taping group are greater than in the Kinesiotaping group.

This study is not free from limitations, as the small sample size, the absence of a means of evaluation for the constancy of the exercises and the application of the bandage by patients and the reduced follow-up period. Lastly, another limitation of the study is that it did not consider tasks other than walking through gait analysis.

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13	nnell Kinesiotaping McConnell	$\pm$ SD Average $\pm$ SD Average $\pm$ SD $\Delta$ T1-T0 $\Delta$ T2-T0 $\Delta$ T3-T0 P value (groups)	0.09 0.65 0.06 0.62 0.07 0.800 0.800 0.800 0.573	0.12 1.27 0.12 1.20 0.12 0.961 0.388 0.715 0.706	0.03 0.09 0.03 0.10 0.02 0.659 0.854 0.715 0.878	0.04 0.40 0.03 0.42 0.03 0.441 0.419 0.572 0.674	0.15 1.10 0.18 1.07 0.13 0.683 0.388 0.464 0.04	7.06 103.37 11.46 103.84 7.69 0.367 0.241 0.272 0.225	5.58 60.25 5.23 53.46 4.51 0.523 0.388 1.000 0.556	6.64 43.88 8.13 40.77 3.90 0.731 0.854 0.272 0.36	1.27 4.37 1.76 3.01 0.92 0.125 0.854 1.000 0.486	7.50 20.94 5.29 19.96 4.02 0.756 0.854 0.272 0.018	4.43 13.85 4.26 12.93 4.72 0.612 0.621 1.000 0.724	0.36 0.84 0.72 0.82 0.28 0.635 0.854 1.000 0.84	0.33 0.56 0.27 0.60 0.23 0.502 0.621 1.000 0.846	0.34 0.86 0.51 0.71 0.26 0.781 0.854 0.272 0.249	0.52 0.82 0.24 0.91 0.29 0.142 0.621 0.715 0.511
T2	Kinesiotaping McConnell	Average ± SD Average ± SD	0.64 0.08 0.61	1.25 0.15 1.24	0.10 0.02 0.09	0.41 0.02 0.40	1.07 0.14 1.03	102.63 7.86 98.92	57.03 6.05 56.77	42.92 5.39 42.04	3.62 1.02 3.97	20.68 7.07 19.56	14.02 4.24 13.60	0.74 0.66 0.59	0.62 0.27 0.47	0.68 0.28 0.72	0.87 0.27 0.81
F	Kinesiotaping McConnell	Average ± SD Average ± SD	0.07 0.62 0.05	0.11 1.20 0.20	0.02 0.10 0.02	0.02 0.42 0.05	0.15 1.07 0.18	11.60 103.84 13.72	6.06 53.46 9.27	4.89 40.77 5.09	1.72 3.01 1.02	7.49 19.96 7.13	4.12 12.93 5.73	1.08 0.82 0.58	0.30 0.60 0.31	0.22 0.71 0.38	0.27 0.91 0.39
ТО	McConnell Kines	Average ± SD Avera	0.62 0.07 0.62	1.21 0.12 1.25	0.10 0.04 0.10	0.40 0.03 0.40	1.02 0.15 1.06	99.69 6.55 102.73	56.63 6.16 57.97	40.69 4.92 41.86	3.59 1.55 4.08	21.00 7.81 22.94	13.62 4.44 13.72	0.69 0.40 0.91	0.51 0.18 0.53	0.98 0.77 0.66	0.97 0.39 0.93
	Kinesiotaping	Average	Step lenght (m) 0.62 0.09	Stride lenght (m) 1.24 0.16	Double support 0.16 0.22 duration (s)	Swing duration 0.40 0.04 (s)	Average speed 1.03 0.19 (m/s)	Frequency 100.15 10.53 cadence (Hz)	ROM Knee 59.55 5.54	ROM Hip 41.67 5.37	ROM Tilt Hip 3.82 1.61 Bone	ROM Hip 22.96 7.11 rotation	ROM Foot 13.80 5.79 rotation	Knee Moment of 0.50 0.20 Flexion (N*m)	Knee Moment 0.45 0.17 of Adduction (N*m)	Hip Moment of 0.86 0.41 Flexion (N*m)	Hip Moment of 0.81 0.21

Legenda. ROM: Range of Motion.

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Table 3. Lower Extremity Function	onal Scale (LEFS) and Nun	meric Pain Rating Scale (NPRS) results.

	то				Т2				ТЗ						
	Kinesiota	ping	McConnell		Kinesiotaping McConnell		ell	Kinesiotaping		McConnell		∆p beetween groups			
	Average ±	± SD	Average	± SD	Average ± SD		Average ± SD		Average ± SD		Average ± SD		∆T2-T0	∆T3- T0	P value (groups)
LEFS	52.31	7.86	52.74	11.12	55.69	11.03	64.42	8.21	62.07	8.38	66.20	14.14	0.188	0.462	<0.01
NPRS	6.88	2.25	6.11	1.33	5.25	1.91	3.84	2.06	4.29	2.23	3.33	2.66	0.945	0.700	<0.01

Legenda. LEFS: Lower Extremity Functional Scale; NPRS: Numeric Pain Rating Scale.

# Table 4. Significance of Gait Analysis data within the groups.

	то		T1		T2		ТЗ		P value			
	Average ± SD		Average ± SD		Average ± SD		Average ± SD		T0-T1	T0-T2	T0-T3	
Average speed (m/s)	1.02	0.16	1.07	0.17	1.04	0.14	1.08	0.15	NS	NS	0.028	
ROM Hip external rotation	21.90	7.46	21.32	7.34	20.07	7.22	19.70	4.72	NS	NS	0.04	

Legenda. ROM: Range of Motion.

Table 5. Significance of Lower Extremity Functional Scale (LEFS) and Numeric Pain Rating Scale (NPRS) within the groups.

		ТО		T2	F	<b>T</b> 3	P value		
	Avera	age ± SD	Avera	ge ± SD	Averaç	ge ± SD	T0-T2	T0-T3	
LEFS	52.54	9.63	60.43	10.43	64.21	11.71	<0.01	<0.01	
NPRS	6.46	1.82	4.49	2.09	3.79	2.47	<0.01	<0.01	

Legenda. LEFS: Lower Extremity Functional Scale; NPRS: Numeric Pain Rating Scale.

# Conclusion

Taken together, the findings of this non-randomized clinical trial showed that the application of the knee bandage for PFPS would appear to show improvement in functioning and biomechanics of patients with PFPS, with better results and significant changes over time in the McConnell taping group than the Kinesiotaping group. Further studies are needed to evaluate the effectiveness of these two methods in the long-term and compare them by considering the analysis of different motor tasks from the gait analysis. Furthermore, it would be useful to verify whether the effectiveness of the bandage may depend on the structural characteristics of the subject.

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#### Authors' contributions

Conceptualization: FA, AdS, and MM; Methodology: FA, AdS, and MM; Investigation: FA, AB, and GA; Formal analysis: FA and MM; Investigation: FA, SV, GA; Statistical analysis: MM; Literature research: CD and GS; Writing—original draft preparation: FA, AdS, and AB; Writing—review and editing: AA, MP, and MM; Visualization: GF, CD, GS, GA; Supervision: FA, AdS, and MM. All the authors read and approved the final version of the manuscript.

#### Declaration of interest

The authors report there are no competing interests to declare.

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